Published in final edited form as:
Psychopharmacology (Berl). 2011 December ; 218(4): 649–665. doi:10.1007/s00213-011-2358-5.

Psilocybin occasioned mystical-type experiences: Immediate and persisting dose-related effects

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Abstract

Rationale—This dose-effect study extends previous observations showing that psilocybin can occasion mystical-type experiences having persisting positive effects on attitudes, mood, and behavior.

Objectives—This double-blind study evaluated psilocybin (0, 5, 10, 20, 30 mg/70 kg, p.o.) administered under supportive conditions.

Methods—Participants were 18 adults (17 hallucinogen-naïve). Five 8-hour sessions were conducted individually for each participant at 1-month intervals. Participants were randomized to receive the four active doses in either ascending or descending order (9 participants each). Placebo was scheduled quasi-randomly. During sessions volunteers used eyeshades and were instructed to direct their attention inward. Volunteers completed questionnaires assessing effects immediately after and 1 month after each session, and at 14 months follow-up.

Results—Psilocybin produced acute perceptual and subjective effects including, at 20 and/or 30 mg/70 kg, extreme anxiety/fear (39% of volunteers) and/or mystical-type experience (72% of volunteers). One month after sessions at the two highest doses, volunteers rated the psilocybin experience as having substantial personal and spiritual significance, and attributed to the experience sustained positive changes in attitudes, mood, and behavior, with the ascending dose sequence showing greater positive effects. At 14 months, ratings were undiminished and were

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consistent with changes rated by community observers. Both the acute and persisting effects of psilocybin were generally a monotonically increasing function of dose, with the lowest dose showing significant effects.

Conclusions—Under supportive conditions, 20 and 30 mg/70 kg psilocybin occasioned mystical-type experiences having persisting positive effects on attitudes, mood and behavior. Implications for therapeutic trials are discussed.

Keywords

psilocybin; dose-effects; hallucinogen; entheogen; psychedelic; mystical experience; fear; spiritual; religion; positive psychology; humans

Introduction

Psilocybin, which is the principal psychoactive component of *Psilocybe* and other genera of mushrooms, has likely been used for millennia within some cultures in structured manners for divinatory or religious purposes (Wasson, 1980; Stamets 1996; Metzner 2004; Guzmán 2008). Like other classic hallucinogens (*d*-lysergic acid diethylamide [LSD], mescaline, *N*,*N*-dimethyltryptamine [DMT]), the effects of psilocybin are primarily mediated at 5-HT_{2A} receptor sites (Glennon et al. 1984; Nichols 2004), and the acute subjective effects include robust changes in perception, cognition, affect, volition, and somesthesia (Isbell 1959; Wolbach et al. 1962; Rosenberg et al. 1964). In early clinical research with psilocybin, the affective character of subjective experiences often varied from positive to negative, and highly valued personal or mystical-type experiences were rare (e.g., Isbell 1959; Malitz et al. 1960; Rinkel et al. 1960; Hollister 1961). Subsequent research that generally used higher psilocybin doses and provided more preparation and interpersonal support reported a higher rate of affectively positive experiences, sometimes of a mystical nature, that were rated as being of personal significance (Leary et al. 1963; Metzner et al. 1965; Pahnke 1969).

Recently, we used rigorous double-blind methods to evaluate the acute (7 hour) and longer-term (2 months and 14 months) psychological effects of a high dose of psilocybin (30 mg/70 kg) relative to an active comparison compound (40 mg/70 kg methylphenidate) in 36 hallucinogen-naïve volunteers (Griffiths et al. 2006, 2008). The study was designed to optimize the potential for positively-valued experiences by providing eight hours of preparation, administering psilocybin in a pleasant, supportive setting, and instructing volunteers to focus explicitly on their subjective or inner experience rather than, for example, perform tasks. The results showed that psilocybin occasioned mystical-type experiences and, sometimes, significant fear. The mystical-type experiences were rated as having substantial and persisting personal meaning and spiritual significance to which volunteers attributed sustained positive changes in attitudes, moods and behavior. The present study was undertaken using similar procedures to characterize the acute and persisting effects of a range of lower doses of psilocybin (0, 5, 10, 20, 30 mg/70 kg). The study was also designed to compare the ascending and descending sequences of drug dose exposure.

Materials and methods

Participants

Participants were recruited from the local community through flyers announcing a study of states of consciousness brought about by psilocybin, a naturally occurring psychoactive substance used sacramentally in some cultures. Two hundred seventy-nine individuals were screened over the telephone and 31 were further screened in person. The 18 study

participants (8 males) were medically healthy (as determined by medical history, physical examination, an electrocardiogram, routine medical blood laboratory tests, and urine testing for common drugs of abuse), psychiatrically healthy, and without family histories of psychotic disorders or bipolar I or II disorder (as determined by structured clinical interviews). Individuals with current alcohol or drug dependence (including nicotine) were excluded, as were individuals with a past history within the past 20 years of alcohol or drug dependence (excluding nicotine). Participants were hallucinogen naïve, except for one who reported using psilocybin mushrooms on two occasions more than 20 years previously. Participants had an average age of 46 years (range 29 to 62) and were well-educated; all had at least some college, 94% were college graduates, and 56% had post-graduate degrees. Fifty-six percent were employed full-time, 33% part-time, and 11% were retired. Fifty percent indicated affiliation with a religious or spiritual community, such as a church, synagogue, or meditation group. While not an inclusion criterion, all 18 volunteers indicated at least intermittent participation in religious or spiritual activities such as religious services, prayer, or meditation, with 39% reporting daily activities and an additional 39% reporting at least weekly activities. Volunteers did not receive monetary compensation for participation. Based on interviews, their motivation for participation was curiosity about the effects of psilocybin and the opportunity for extensive self-reflection in the context of the day-long drug sessions and the meetings with the monitors that occurred before and after sessions. The Institutional Review Board of the Johns Hopkins University School of Medicine approved the study, and all volunteers gave their informed consent before participation.

Study design and overview

The study procedures followed recommendations provided for safe conduct of research administering high doses of a classic hallucinogen (Johnson et al. 2008). The study examined psilocybin (0, 5, 10, 20, and 30 mg/70 kg) using a double-blind, between-group, crossover design that involved five 8-hour drug sessions conducted at approximately 1-month intervals, and a 14-month follow-up. Eighteen volunteers were randomly assigned to receive the active psilocybin doses in either an ascending dose sequence or a descending sequence. Although each volunteer received the 0 mg/70 kg condition once, across the 9 volunteers in each of the ascending and descending sequences, the 0 mg/70kg condition occurred twice on sessions 1, 2, 4, and 5, and once on session 3. The purpose of this quasi-random scheduling of placebo was to obscure the dose sequence to the participants and monitors (see Instructions section below). Outcome measures obtained throughout the drug sessions included blood pressure and monitor ratings of participant mood and behavior. At about 7 hours after drug ingestion (when the primary drug effects had subsided), participants completed several questionnaires designed to assess various aspects of hallucinogen experience (described below). Various longitudinal and persisting effects measures were assessed at screening, 1 month after each drug session, and at 14 months after the last session.

Instructions to participants and monitors

Participants and monitors were informed that participants would receive placebo and four different doses (ranging from low to high) of psilocybin in mixed order across sessions. Neither participants nor monitors were informed that the active psilocybin doses would be tested in an ascending or descending sequence. The only exception to this was that two of the seven assistant monitors were not blind to the ascending/descending nature of the experimental design, however they were blind to the outcome of randomization.

Drug conditions

Psilocybin doses and placebo (0 mg/70 kg) were prepared in identically-appearing opaque, size 0 gelatin capsules, with lactose as the inactive capsule filler. On each session, a single capsule was administered with 180 ml water.

Meetings with monitor before and after sessions

The primary monitor (usually along with the assistant monitor) met with each participant on four occasions before his or her first session (for 8 hours total), once for about an hour on the day following each of the five sessions, and one more time about 3 weeks after each session. The purpose and content of these meetings are described elsewhere (Griffiths et al. 2006; Johnson et al. 2008). Monitors and assistant monitors were trained by personnel with extensive prior experience monitoring hallucinogen sessions.

Drug Sessions

As described in more detail previously (Griffiths et al. 2006), drug sessions were conducted in an aesthetic living-room-like environment with two monitors present. Participants were instructed to consume a low-fat breakfast before coming to the research unit. A urine sample was taken to verify abstinence from common drugs of abuse (cocaine, benzodiazepines, and opioids including methadone). Although the presence of THC was not tested, none of the volunteers reported recent use of cannabis. For most of the time during the session, participants were encouraged to lie down on the couch, use an eye mask to block external visual distraction, and use headphones through which a music program was played. The same music program was played for all participants in all sessions. Participants were encouraged to focus their attention on their inner experiences throughout the session.

Measures assessed throughout the session

Ten minutes before and 30, 60, 90, 120, 180, 240, 300, and 360 minutes after capsule administration, blood pressure, heart rate, and monitor ratings were obtained.

Blood pressure and heart rate—Blood pressure (systolic and diastolic pressure using oscillometric method with the blood-pressure cuff placed on the arm) and heart rate were monitored using a Non-Invasive Patient Monitor Model 507E (Criticare Systems, Inc., Waukesha, WI).

Monitor Rating Questionnaire—At the same time-points at which the physiological measures were taken, the two session monitors completed the Monitor Rating Questionnaire, which involved rating or scoring several dimensions of the participant's behavior or mood (Table 1). The dimensions that are expressed as peak scores in Table 1 were rated on a 5-point scale from 0 to 4. Dimensions expressed as total duration in Table 1 were rated as the estimated number of minutes since the last rating. Data were the mean of the two monitor ratings at each time-point.

Measures assessed 7 hours after drug administration

At about 7 hours after capsule administration when the major drug effects had subsided, the participant completed three questionnaires developed for assessing the subjective effects of hallucinogen drugs and two questionnaires developed for assessing mystical experience. Participants typically completed these questionnaires in about 40 minutes.

Hallucinogen Rating Scale—This 99 item questionnaire, which was designed to show sensitivity to the hallucinogen N,N-dimethyltryptamine (DMT) (Strassman et al. 1994),

consists of six subscales assessing various aspects of hallucinogen effects (Intensity, Somaesthesia, Affect, Perception, Cognition, and Volition).

APZ—The APZ is a 72 item yes/no questionnaire designed to assess altered states of consciousness, including those produced by hallucinogens (Dittrich 1998). The three major scales on the APZ are the OSE (oceanic boundlessness; a state common to classic mystical experiences including feelings of unity and transcendence of time and space), the AIA (dread of ego dissolution; dysphoric feelings), and the VUS (visionary restructuralization; includes items on visual pseudo-hallucinations, illusions, and synesthesias). Data on each scale were expressed as a proportion of the maximum possible score.

Addiction Research Center Inventory (ARCI)—The ARCI was developed to differentiate subjective effects among several classes of psychoactive drugs including the hallucinogens (Haertzen 1966). The short form of the ARCI consists of 49 true/false questions and contains five major scales: lysergic acid diethylamide (LSD), a hallucinogen-sensitive scale that is often interpreted as providing a measure of dysphoric changes; pentobarbital, chlorpromazine, alcohol group (PCAG), a sedative sensitive scale; benzedrine group (BG) and amphetamine (A) scales, amphetamine-sensitive scales; and morphine-benzedrine group (MBG), often interpreted as a measure of euphoria (Martin et al. 1971; Jasinski 1977). Participants were instructed to answer the questions on the ARCI with reference to the effects they experienced since they received the capsule that morning.

States of Consciousness Questionnaire—This 100 item questionnaire is rated on a 6-point scale [0=none; not at all; 1=so slight cannot decide; 2=slight; 3=moderate; 4=strong (equivalent in degree to any previous strong experience or expectation of this description); 5=extreme (more than ever before in my life and stronger than 4)]. Forty-three items on this questionnaire comprised the current version of the Pahnke-Richards mystical experience items, which was shown sensitive to psilocybin (Electronic Supplementary Table 1 in Griffiths et al. 2006). An earlier version of this scale was also previously shown sensitive to psilocybin and other hallucinogens (Pahnke 1963; Turek et al. 1974; Richards et al. 1977). The 43 items provide scale scores for each of seven domains of mystical experiences: internal unity (pure awareness; a merging with ultimate reality); external unity (unity of all things; all things are alive; all is one); sense of sacredness (reverence; sacred); noetic quality (claim of an encounter with ultimate reality; more real than everyday reality); transcendence of time and space, deeply-felt positive mood (joy, peace, love); paradoxicality and ineffability (claim of difficulty in describing the experience in words). Data on each domain scale were expressed as a percentage of the maximum possible score. As in previous studies (Pahnke 1969; Griffiths et al. 2006), criteria for designating a volunteer as having had a “complete” mystical experience were that scores on each of the following six scales had to be at least 60%: unity (either internal or external, whichever was greater), sense of sacredness, noetic quality, transcendence of time and space; positive mood; and ineffability. A mean total score was calculated as a mean of all items from the preceding six scales. The remaining 57 items in the States of Consciousness Questionnaire served as distracter items.

Mysticism Scale (Experience-specific)—This 32-item questionnaire, which assesses primary mystical experiences, has been extensively studied and shows cross-cultural reliability (Hood et al. 2001, 2009) and has previously been shown sensitive to psilocybin (Griffiths et al. 2006). A total score and three empirically-derived factors are measured: Interpretation (corresponding to three mystical dimensions: noetic quality, sacredness, and deeply felt positive mood); Introvertive Mysticism (corresponding to the mystical dimensions of internal unity, transcendence of time and space, and ineffability); Extrovertive Mysticism (corresponding to the dimension of the unity of all things/all things are alive).

Items were rated on a 9-point scale (Griffiths et al. 2006). For this experience-specific version of the questionnaire used 7 hours after drug administration, participants were instructed to complete the questionnaire with reference to their experiences since they received the capsule that morning.

Persisting effects assessed one month after sessions

At 3 to 4 weeks after each session, and before any additional session, participants returned to the research facility and completed a series of questionnaires to assess possible changes in various standardized measures of personality, mood, and spirituality (not included in this report) as well as possible persisting changes in attitudes, mood, behavior, and spirituality. Participants typically completed these questionnaires in about 75 minutes.

Persisting Effects Questionnaire—This 143-item questionnaire sought information about changes in attitudes, moods, behavior, and spiritual experience that, on the basis of prior research (Pahnke 1969; Doblin 1991, Griffiths et al. 2006), would be sensitive to the effects of psilocybin a month after the session. One hundred forty of the items were rated on a 6-point scale (0=none, not at all; 1=so slight cannot decide; 2=slight; 3=moderate; 4=strong; 5=extreme, more than ever before in your life and stronger than 4). Within the questionnaire, the items were labeled in six categories: Attitudes about life (13 positive and 13 negative items); Attitudes about self (11 positive and 11 negative items); Mood Changes (9 positive and 9 negative items); Relationships (9 positive and 9 negative items); Behavioral changes (1 positive and 1 negative item); Spirituality (22 positive and 21 negative items). The positive and negative items were intermixed within each category. For purposes of scoring the resulting 12 scales (positive and negative scales for each of 6 categories) scores were expressed as the percentage of the maximum possible score. The version of the questionnaire used (available from the authors upon request) was an expanded version of that described by Griffiths et al. 2006. Scale scores on the original and the expanded version were highly correlated (.958-.997) on scales showing reasonable variability. Scales measuring negative effects did not have enough responses and therefore did not have enough variability for these calculations to be meaningful.

The questionnaire included three additional questions (see Griffiths et al. 2006 for more specific wording): 1). How personally meaningful was the experience? (rated from 1-8, with 1=no more than routine, everyday experiences; 7=among the 5 most meaningful experiences of my life; and 8=the single most meaningful experience of my life). 2). Indicate the degree to which the experience was spiritually significant to you? (rated from 1 to 6, with 1=not at all; 5=among the 5 most spiritually significant experiences of my life; 6=the single most spiritually significant experience of my life). 3). Do you believe that the experience and your contemplation of that experience have led to change in your current sense of personal well-being or life satisfaction? (rated from +3=Increased very much; 0=No change; −3=Decreased very much).

Retrospective persisting effects assessed at 14-month follow-up

At 14 months after the last session, participants completed a Retrospective Questionnaire and an open-ended clinical interview reflecting on study experiences and current life situation. For purposes of completing the Retrospective Questionnaire, volunteers were reminded that over the 5 sessions they had received 4 different doses of psilocybin. They were then informed on which two sessions they had received the two highest doses of psilocybin, although they were not informed which of the two was the highest dose. One hundred forty-three items comprised the previously described Persisting Effects Questionnaire. For these items, volunteers were asked to rate any current persisting effects that they attribute to the experiences during either or both the two highest dose sessions.

Volunteers were also asked to provide written descriptions about the session experiences, including how their behavior changed in response to the experiences. Forty-three items on this questionnaire were the previously described mystical experience items from the States of Consciousness Questionnaire, which were completed twice -- looking back separately on each of the two sessions associated with the two highest doses. In four final questions, participants were asked, of all five sessions, which session was associated with the strongest effect, which was most personally meaningful, which was most spiritually significant, and which would they chose to repeat if they had the opportunity to do so.

Longitudinal measures assessed at baseline, after session 5, and at 14-month follow-up

More than a dozen longitudinal measures were assessed at screening or shortly after enrollment, after sessions, and at the 14-month follow-up. The results from most of these measures will be combined with results from a previous study (Griffiths et al. 2006) and reported separately. Three measures are reported here.

Mysticism Scale (Lifetime)—Participants were instructed to complete this previously described questionnaire with reference to their lifetime experience.

Death Transcendence Scale—The 26-item Death Transcendence Scale (Hood and Morris, 1983; VandeCreek, 1999) was administered because a potentially important clinical application of psilocybin is in treatment of individuals who are anxious or depressed in response to terminal illness (Grob et al. 2011). Items were rated on a 9-point scale and five subscales were scored: Mysticism, Religious, Nature, Creative, and Biosocial.

Community Observer Ratings of Changes in Participants' Behavior and Attitudes—This previously described measure was shown sensitive to psilocybin 2 months after a high dose session (Griffiths et. al., 2006). After acceptance into the study, each participant designated as raters three adults who were expected to have continuing contact with the participant (e.g. family members, friends, or colleagues at work). Ratings were conducted via a structured telephone interview approximately 1 week after the participant had been accepted into the study, 3 to 4 weeks after the last session, and as part of the 14-month follow-up. The interviewer provided no information to the rater about the participant. The structured interview consisted of asking the rater to rate the volunteer's behavior and attitudes using a 10 point scale (from 1=not at all, to 10=extremely) on eleven items: inner peace; patience; good-natured humor/playfulness; mental flexibility; optimism; anxiety; interpersonal perceptiveness and caring; negative expression of anger; compassion/social concern; expression of positive emotions (e.g. joy, love, appreciation); and self-confidence. On the first rating occasion, which occurred soon after acceptance into the study, raters were instructed to base their ratings on observations of and conversations with the participant over the past 3 months. On subsequent assessments, raters were told their previous ratings and were instructed to rate the participant based on interactions over the last several weeks. Data from each interview with each rater were calculated as a total score, with anxiety and anger scored negatively. Changes in each participant's behavior and attitudes after drug sessions were expressed as a mean change score (i.e. difference score) from the baseline rating across the raters. Rating completion rate was 96%; seven ratings were missed due to a failure to return calls or to the rater not having contact with the volunteer over the rating period.

Post-study monitor ratings of enduring effects in participants

At the conclusion of the study, the primary and assistant monitor for each volunteer were asked to assess any enduring changes in the volunteer's attitudes and behaviors that the monitor believed resulted directly or indirectly from the psilocybin session experiences in the study. Three ratings were done on a 7-point scale (−3=decreased very much; 0=No

change; +3=increased very much): 1. Change in volunteer's sense of personal well-being or life satisfaction; 2. Change in quality of volunteer's social relationships (e.g. spouse, family, friends and acquaintances); and 3. Change in the volunteer's sense of spirituality, broadly construed. Score for each volunteer was the mean of the primary and assistant guide ratings for each question.

Data Analyses

Cardiovascular and Monitor Ratings assessed throughout the session—Two sets of analyses were conducted. For the time-course data, Planned Comparisons were conducted comparing the effect of each of the active psilocybin doses with 0 mg/70 kg at each time-point. For the second set of analyses, for each participant, peak scores during the time-course were defined as the maximum value from pre-capsule to 6 hr post-capsule, and temporal measures (e.g. minutes talking or sleeping) were summed across the 8 post-capsule time-points. A repeated measures regression model with AR(1) covariance structure was used with Dose (0, 5, 10, 20, 30 mg/70 kg), Time (10 min before and 0.5, 1, 1.5, 2, 3, 4, 5, and 6 hr after capsule administration), Dose Sequence (ascending vs. descending), and interactions among these as the effects in the model. Fisher's LSD post-hoc tests were used to compare the drug conditions. Two of the seven assistant guides were not blind to the ascending/descending nature of the experimental design, so the analysis described above was repeated excluding ratings from these two monitors. Because there were no differences in the statistical significance of Sequence or Sequence interactions and only minor other differences occurred, the data presented are from all monitor ratings.

Measures assessed 7 hours after drug administration and measures assessed one month after sessions—For the hallucinogen-sensitive questionnaires and the mystical experience questionnaires assessed 7 hours after sessions and for the Persisting Effects Questionnaire assessed one month after sessions, a repeated measures regression was used with Dose (0, 5, 10, 20, 30 mg/70 kg) and Dose Sequence (ascending vs. descending) and their interaction as effects in the model. Fisher's LSD post-hoc tests were used to compare the drug conditions. For analysis of dichotomous responses across the five drug conditions for measures shown in Table 5 (Persisting Effects Questionnaire), Cochran's Q, a non-parametric, binary repeated measures test, was conducted with a factor of Dose (0, 5, 10, 20, 30 mg/70 kg). Planned comparisons for these data were conducted using Wald chi square tests to compare active doses to 0 mg/70 kg.

Retrospective persisting effects assessed at 14 month follow-up—For analysis of the eight scales from the mystical experience items of the States of Consciousness Questionnaire, a repeated measures regression was used with Condition (7 hours after 0 mg/70 kg; 7 hours after 30 mg/70 kg; and 14 month retrospective for 30 mg/70 kg), Dose Sequence, and their interaction as effects in the model. Fisher's LSD post-hoc tests were used to compare the conditions. For analysis of dichotomous responses across three sets of conditions (1 month after 0 mg/70 kg; combined data for 1 month follow-ups after both the 20 and 30 mg/70 kg dose sessions; 14 month follow-up data for retrospective rating for either or both the 20 and/or 30 mg/70 kg dose sessions), Cochran's Q was conducted with a factor of Condition (the three conditions described above). Planned comparisons were conducted using Wald chi square tests to compare the three conditions.

Longitudinal measures assessed at screening, after session 5, and at 14-month follow-up—For analysis of the measures of mystical experience, of death transcendence, and of community observer ratings of changes in participants' behavior and attitudes assessed at screening, 1 month after session 5, and at 14-month follow-up, a repeated measures regression was used with Time (screening, after session 5, and 14-month

follow-up) and Dose Sequence and their interaction as effects in the model. Planned comparisons were used to compare screening values with the two post-drug time points.

For all statistical analysis, results were considered significant at $p < .05$.

Results

Integrity of blinding procedures

At the conclusion of the study, the primary and assistant guides completed a questionnaire that asked about their understanding of the experimental design. None of the three primary guides or the five assistant guides who were blind the ascending or descending nature of the doses sequences guessed or reported awareness of this aspect of the study procedures.

Cardiovascular measures and monitor ratings assessed throughout the session

Psilocybin produced significant and orderly dose- and time-related effects on cardiovascular measures and monitor ratings assessed throughout the session. At the two highest doses (20 and 30 mg/70kg), onset of significant effects generally occurred at the 30- or 60-minute assessment, with effects usually peaking from 90 to 180 minutes and decreasing toward pre-drug levels over the remainder of the session (see Figure 1 for illustrative measures). Table 1 shows the mean effects at each dose for these measures. For measures sensitive to psilocybin, effects were generally a monotonically increasing function of dose. For most measures, the 5 mg/70 kg dose was significantly greater than placebo and the 20 and/or 30 mg/70 kg dose(s) were significantly greater than the lower active doses. There were no significant Sequence or Dose x Sequence interactions. The blood pressures of the four volunteers who had the highest pressures 60 minutes or longer after the 30 mg/70 kg psilocybin were: 187/84, 166/64, 182/88, and178/95 mmHg. These pressures were considered high enough to warrant further repeated blood pressure assessment, however they were not judged to be of sufficient magnitude to necessitate pharmacological treatment.

Drug effect and mysticism measures assessed 7 hours after drug administration

Subjective effects questionnaires—The three questionnaires developed for sensitivity to the subjective effects of hallucinogens showed orderly dose-related increases (Table 2). All six scales of the Hallucinogen Rating Scale, all three scales on the APZ Questionnaire, and the A and LSD scales of the ARCI showed significant and monotonically increasing effects as a function of dose, with significant effects on most measures at even the lowest dose of 5 mg/70 kg. These effects, which are typical of hallucinogens, include perceptual changes (e.g. visual pseudo-hallucinations, illusions, and/or synesthesias), labile moods (e.g. feelings of transcendence, grief, joy, and/or anxiety), and cognitive changes (e.g. sense of meaning, insight, and/or ideas of reference). There were no significant Sequence or Sequence x Dose interactions.

Measures of mystical experience—Also at 7 hours after capsule administration, volunteers completed two questionnaires designed to assess mystical experience (Table 3). The total score and all three empirically-derived factors of the Mysticism Scale and all seven scales on States of Consciousness Questionnaire showed significant and monotonically increasing effects as a function of dose, with significant effects at the 5 mg/70 kg dose. The proportion of volunteers who met *a priori* criteria for having had a “complete” mystical-type experience on the States of Consciousness Questionnaire was also an increasing function of dose: 0, 5.6, 11.1, 44.4, and 55.6% at 0, 5, 10, 20, and 30 mg/70kg, respectively. Overall, 72.2% of volunteers had “complete” mystical experiences at either or both the 20 and 30 mg/70 kg session. Only the Mysticism Scale showed an effect of Sequence or a Dose x Sequence interaction. This effect was largely due to differences in response to placebo.

Examination of the position of the placebo condition within the sequence suggested this result was spurious.

Psilocybin-Induced Fear/Anxiety or Delusions

Although volunteers were carefully screened and psychologically prepared, and close interpersonal support was provided during sessions, on questionnaires completed at the end of the session, 39% of participants (7 of 18) had extreme ratings of fear, fear of insanity or feeling trapped at some time during the session. Such episodes occurred in 6 of 7 of these participants after the 30 mg/70 kg dose and in 1 of 7 after the 20 mg/70 kg dose. Monitor ratings of peak anxiety/fear during the session showed dose-rated increases, with each dose producing a significantly higher rating than the lower doses (Table 1). After 30 mg/70 kg, monitor ratings of anxiety/fear across the session showed varying time-courses of onset and duration, with peak effects of anxiety/fear being rated as early as 60 minutes in some participants, but as late as 180 or 240 minutes in others (see Figure 2 for illustrative data). Forty-four percent of participants (8 of 18) reported delusions or paranoid thinking sometime during the session; such episodes occurred in 7 of 8 of these participants after the 30 mg/70 kg dose and in 1 of 7 after 20 mg/70 kg dose. Examples of delusions included the belief that a child or loved one had died during the time of the session, or that the session monitors were malevolently manipulating the participant. Three of 8 volunteers who had such episodes were those who also rated extreme fear or fear of insanity. Inspection of the data indicated that delusions and extreme ratings of fear/anxiety were not differentially affected by dose sequence.

These psychological struggles did not affect the overall rate of having “complete” mystical experiences as rated by volunteers at the end of the session day. Five of seven (71%) of participants reporting extreme fear, insanity or feeling trapped provided data consistent with “complete” mystical experiences, and 4 of 8 (50%) of participants who had delusions or paranoid thinking provided data consistent with “complete” mystical experiences. These rates of “complete” mystical experience are generally similar to the rate for the group as a whole (56%). Although psychological struggles did not affect the overall rate of “complete” mystical experience, it should be noted that neither of the two volunteers who had the most sustained anxiety during the 30 mg/70 kg session (Figure 2, square and circle symbols) had a “complete” mystical experience. In addition to not affecting rate of mystical experience, inspection of the data indicated no consistent relationship between psychological struggle and subsequent ratings of the session as having personal meaning and spiritual significance. No volunteer rated the overall experience as having decreased her or his sense of well-being or life satisfaction.

The volunteer who had the most sustained anxiety during the 30 mg/70 kg dose session (Fig. 2, square symbols) provides an interesting case example. Likely as a consequence of the sustained psychological struggle during the session, this volunteer also had the lowest mystical experience rating immediately after the session of all 18 volunteers studied. Immediately after the session, this volunteer, who for decades had held reincarnation as part of her worldview, reported that it was the worst experience of her life and that she would rather spend three lifetimes on a mountaintop meditating than repeat what she had just experienced during the session. Although she considered dropping out of the study after this first session and she remained hesitant to receive psilocybin again, over the next several weeks she increasingly felt that she had learned something useful from the experience. At 1 month, she rated the experience as having slight spiritual significance and as having slightly increased her sense of well-being or life satisfaction. Because she remained curious about the effects of psilocybin, she decided to continue to participate in the study. She received 20 mg/70 kg psilocybin on the second session. In contrast to her first session, her post-session ratings fulfilled criteria for a “complete” mystical experience and, at 1 month, she

retrospectively rated this experience as the single most personally meaningful and spiritually significant of her life.

Persisting effects assessed one month after sessions

Persisting Effects Questionnaire—As shown in Table 4, psilocybin produced significant and generally monotonically increasing effects as a function of dose in positive ratings of attitudes about life, attitudes about self, mood, social effects, and behavior. Negative ratings of these same dimensions were very low and did not differ across the doses except for negative attitudes about self that showed small but significant increases at the two lowest doses. Table 4 also shows that ratings of the personal meaningfulness and spiritual significance of the experience, and ratings of well-being or life satisfaction were significant and a monotonic increasing function of dose. Of the persisting effects measures shown in Table 4, all six of the positive subscales (attitudes about life, attitudes about self, mood, altruism, behavior, and spirituality) and one of the three questions (sense of well-being/life satisfaction) showed significant Dose x Dose Sequence interactions. Inspection of these data showed that this effect was primarily due to the ascending dose sequence producing relatively larger effects at the 20 and 30 mg/70 kg doses and relatively smaller effects at lower doses compared to the descending dose sequence. Figure 3 shows this effect for two representative measures: persisting effects on well-being/life satisfaction and on positive mood.

Table 5 shows the percentages of volunteers who endorsed specific outcomes on four items on the Persisting Effects Questionnaire. Endorsement increased as a function of dose. Notably, 61% of volunteers considered the psilocybin experience during either or both the 20 and 30 mg/70 kg sessions to have been the single most spiritually significant of their lives, with 83% rating it in their top 5. Consistent with this, 94%, and 89% of volunteers, respectively, indicated that the experiences on those same sessions increased their well-being or life satisfaction and positively changed their behavior at least moderately. Of the 90 total sessions, none were rated as having decreased well-being or life satisfaction.

Retrospective persisting effects assessed at 14-month follow-up

The right-most columns of Tables 3, 4 and 5 show that the retrospective ratings at the 14-month follow-up on the States of Consciousness Questionnaire mystical experience items and on the Persisting Effects Questionnaire were undiminished from ratings obtained 1 month after sessions. No participant rated that their behavior was affected negatively or that their well-being/life satisfaction was decreased as a result of the psilocybin experiences on the two highest dose sessions. The analysis of the States of Consciousness Questionnaire mystical experience items showed significant Condition x Dose Sequence Interactions on Internal Unity, Mood, and Total score. Inspection of these data showed that the ascending dose sequence was associated with relatively larger effects at 30 mg/70 kg both post-session and at 14-month follow-up.

When asked at 14 months which of the five sessions seemed strongest, 83% and 17% of volunteers indicated the session associated with 30 and 20 mg/70 kg, respectively; most personally meaningful (44%, 44%, and 11% at 30, 20, and 10 mg/70 kg, respectively); most spiritually significant (56%, 33%, and 11% at 30, 20, and 10 mg/70 kg, respectively); and which session they would want to repeat if they had an opportunity to do so (67%, 28% and 6% at 30, 20 and 10 mg/70 kg, respectively). Consistent with the flattened dose-effect curve for persisting effects shown in Fig. 3, most volunteers in the ascending dose sequence rated the highest dose session (30 mg/70 kg) as the most personally meaningful (67%) and spiritually significant (78%) of the five sessions; in contrast, a smaller proportion of volunteers in the descending sequence rated the highest dose session as most personally

meaningful (22%) and spiritually significant (22%). The mean ± 1 SEM dose of the sessions that were rated as being the most personally meaningful were 25.6 ± 2.6 and 21.1 ± 1.8 in the ascending and descending dose sequence, respectively (N.S.); similar ratings of spiritual significance were 27.8 ± 2.6 and 21.1 ± 1.5 respectively ($p<.05$, t-test).

Also at the 14-month follow-up, participants provided written descriptions, based on their memories of their two highest dose sessions, of how they thought their behavior changed in response to those experiences. As summarized in Table 6, only 2 volunteers indicated no positive change in their behavior. The domains of change most frequently cited were better social relationships with family and others, increased physical and psychological self-care, and increased spiritual practice.

Longitudinal measures assessed at baseline, after session 5, and at 14-month follow-up

Longitudinal measures of mystical experience, of death transcendence, and of community observer ratings of changes in participants' behavior and attitudes showed effects generally consistent with the previously described persisting effects. After session 5 and at 14-month follow-up, the total score (as well as each of the three subscales) of the Mysticism Scale (Lifetime) was significantly higher than at screening (217.9 ± 10.8, 264.1 ± 6.8, and 260.4 ± 7.6, means and SEMs for total scores at screening, post-session 5, and 14-month follow-up, respectively)(Planned comparisons, $p<.0001$). The Religious subscale of the Death Transcendence Scale, which assesses a sense of continuity after death, showed similar increases (28.72 ± 1.57, 31.00 ±, 0.99, and 31.28 ± 1.07, means and SEMs for screening, post-session 5, and 14-month follow-up, respectively)(Planned comparisons, $p<.05$). The other subscales were not significant. For the community observer ratings of participants' behavior and attitudes, change scores from those taken about 1 week after study enrollment (means ± SEMs) were significant both after session 5 (8.85 ± 1.64) and at the 14-month follow-up (5.36 ± 1.68)(Planned comparisons, $p<.001$).

Post-study monitor ratings of enduring effects in participants

The post-study monitor ratings of enduring effects in participants were consistent with the participant self-ratings and the community observer ratings of changes in participants' behavior and attitudes. Mean ± SEM of monitor ratings of the volunteers' personal well-being/life satisfaction, quality of social relationships, and sense of spirituality were all in the positive direction (2.33 ± 0.14, 1.64 ± 0.14, and 2.41 ± 0.15, respectively).

Open-ended clinical interview at the 14-month follow-up

An open-ended clinical interview at the 14-month follow-up was conducive to the spontaneous reporting of possible persisting adverse events. There were no reports of bothersome or clinically significant persisting perception phenomena sometimes attributed to hallucinogen use. Likewise, there were no reports of any non-study use of hallucinogens since study enrollment. All 18 volunteers appeared to continue to be psychiatrically healthy, high-functioning, productive members of society.

Discussion

The present study demonstrated orderly dose-related increases in the effects of psilocybin on volunteer and observer ratings of drug effect and on the cardiovascular measures of blood pressure and heart rate. Notably, even the 5 mg/70 kg (71 μg/kg) dose of psilocybin produced significant subjective, physiological, and observer-rated effects. This is the lowest dose of psilocybin demonstrated to produce significant effects. A previous study showed dose-related effects of psilocybin at doses of 45, 115, 215, and 315 μg/kg, however did not show statistically significant effects at the lowest dose (Hasler et al. 2004). Consistent with

previous findings, the present study showed orderly time-related observer-rated and cardiovascular effects during the session, with significant effects at the highest doses generally occurring at 30-60 minutes, peaking at 90-180 minutes, and decreasing toward pre-drug levels over the remainder of the session (Griffiths et al. 2006).

The present study extends previous observations showing that psilocybin can occasion mystical-type experiences having sustained personal and spiritual significance (Pahnke 1963; Doblin 1991; Griffiths et al. 2006, 2008). Two volunteer-rated measures of mystical-type experience completed at the end of the session days showed dose-related increases, with 72% of volunteers fulfilling criteria for having had a “complete” mystical experience at either or both of the two highest dose sessions. Retrospective ratings of mystical experience and spiritual significance did not diminish in time. One month after either or both the two highest dose sessions, 83% of participants rated the experience as the single most or among the 5 most spiritually significant experiences of their life. At the 14-month follow-up, this number was even higher (94%). Likewise, at 14 months, retrospective ratings of mystical experience at the highest dose were generally slightly higher than at the 1-month rating time. Finally, longitudinal measures of lifetime mystical experience and of death transcendence (Religious subscale) were significantly increased over screening levels at both one month and 14 months after the final session. The significant increase in the Religious subscale of the Death Transcendence Scale is notable in this group of healthy volunteers because questions in this subscale assess a sense of continuity after death (e.g. Death is a transition to something even greater than this life; Death is never just an ending, but a part of a process). This effect may be relevant to the proposed palliative effects of psilocybin and similar hallucinogens in treating existential anxiety in terminal illness (Kast 1967; Richards et al. 1972; Grob et al. 2011).

The present study also extends previous observations indicating that psilocybin can occasion persisting positive changes in attitudes, mood, life satisfaction, behavior, and altruism/social effects (Griffiths et al. 2006, 2008). All of these domains showed dose-related increases one month after sessions, with effects at the highest doses sustained at the 14-month follow-up. One month after sessions at either or both the two highest dose sessions, 94% of volunteers endorsed that the experience increased their sense of well-being or life satisfaction moderately or very much, and 89% rated moderate or higher changes in positive behavior. At the 14-month follow-up, these ratings remained high. The types of behavior change most frequently cited by volunteers were better social relationships with family and others, increased physical and psychological self-care, and increased spiritual practice (Table 6). Ratings by community observers before and after the study as well as ratings by study monitors after the study were consistent with the persisting positive changes in behavior and attitudes claimed by the volunteers. The persisting positive changes, particularly in attitudes, mood, and life satisfaction, occasioned by psilocybin appear similar in kind and breadth to the enduring changes reported in case studies of individuals who have had spontaneously-occurring mystical- or insightful-types of experiences (Miller and C’ de Baca, 2001).

A novel aspect of the present study was that it compared effects in volunteers who received the four active psilocybin doses in either an ascending or a descending dose sequence. Although the acute measures of psilocybin effects were not affected by the dose sequence, volunteer-rated positive changes in attitudes and behavior assessed 1 month after each session showed Dose x Dose Sequence interactions reflecting relatively larger effects at the highest psilocybin doses than the lower doses in the ascending dose sequence compared to the descending sequence (Figure 2). Analogous differences occurred at the 14-month follow-up assessment on the mystical experience items of the States of Consciousness Questionnaire and on retrospective ratings of the personal meaning and spiritual significance associated with various session doses. Overall, these findings suggest that the ascending

dose sequence is somewhat more likely than the descending sequence to produce long-lasting positive changes in attitudes, behavior, and remembered mystical-type experiences. Thus it appears that having experience with lower doses facilitates the likelihood of having sustained positive effects after a high dose of psilocybin. The biological or psychological mechanisms underlying this effect are unknown. This finding suggesting an advantage of an ascending dose sequence may have clinical application in the design of therapeutic studies of psilocybin (Griffiths and Grob, 2010; Grob et al. 2011). It is noteworthy, however, that this finding is contrary to some older recommendations of psychotherapists who administered classic hallucinogens. Specifically, in one report (Blewett and Chwelos, 1959) psychotherapists inferred from their clinical experience that a single high-dose overwhelming experience was more therapeutic than an approach that began with a small doses and gradually increased the dose over successive experiences.

Also of relevance to the design of future research trials with psilocybin, the present study provides information about the relative likelihood of different doses of psilocybin to occasion acute adverse subjective effects as well as mystical-type effects having persisting positive effects. The acute anxiety/fear-producing effects of psilocybin, as assessed by monitor and volunteer ratings, increased with increasing doses. Thirty-nine percent of volunteers reported extreme fear, fear of insanity, or feeling trapped sometime during the session (0 at placebo or the two lower doses, 1 at 20 mg/70 kg, and 6 at 30 mg/70 kg). Furthermore, 44% of volunteers reported delusions or paranoid thinking sometime during the session (0 at placebo and the two lower doses, 1 at 20 mg/70 kg, and 7 at 30 mg/70 kg). In the present study, such negative effects were well managed with reassurance in the highly supportive setting. Interestingly, these psychological struggles did not generally affect rates of having “complete” mystical experiences, possibly because the negative feelings were most often of short duration. However, under conditions in which volunteers are less well screened and psychologically prepared, or sessions are not as well supervised, there could be a possibility that extreme anxiety and/or delusion could be prolonged and result in dangerous behavior. Under such conditions, administration of doses higher than about 20 mg/70 would be inadvisable. The unpredictable time-course across the session of anxiety or fear (Fig.2) underscores the importance that session monitors remain vigilant throughout the session. Furthermore, the unpredictable time-course of anxiety, in combination with the finding that even experienced session monitors cannot rate with high reliability whether or not psilocybin has been administered (Griffiths et al., 2006), suggests the potential risk of the recommendation by some psychotherapists that a “booster” dose of a classic hallucinogen should be administered relatively shortly after the initial dose if the effects are less than expected (Blewett and Chwelos, 1959; Stolaroff 1997).

In a therapeutic or other research trial, the possibility of such potentially adverse effects should be considered in relationship to the potential persisting positive effects. The proportion of volunteers having “complete” mystical-type experiences, which likely mediate persisting positive effects (Richards et al. 1977; Griffiths et al. 2008), as well as the persisting positive effects (Table 4 and 5) were generally an increasing function of dose, with the percentage change from 20 to 30 mg/70 kg varying widely (−23% to a +99%), with a mean of +17%. However, endorsement of having had a “complete” mystical experience, or of having had the single most spiritually significant experience of his/her life increased 25% and 60%, respectively from 20 to 30 mg/70 kg. Likewise, endorsement of moderate to extreme positive behavioral change, which may be the most relevant outcome measure in some therapeutic trials, increased 45% from 20 to 30 mg/70 kg. Thus, in addition to considering the extent of screening and support provided to volunteers, the decision to administer psilocybin doses higher than about 20 mg/70 kg should be made on the basis of the type of outcome desired.

The present study provided no evidence of adverse effects of high dose psilocybin exposure other than the episodes of psychological struggle during some portion of the time of psilocybin action. This should not be interpreted to suggest that casual use of high dose psilocybin is safe. It is important to recognize that the present study was conducted in carefully screened volunteers who received ample preparation before sessions, were closely monitored during sessions, and had some continuing contact with study staff after sessions (see Johnson et al., 2008 for detailed safety guidelines for minimizing risks of high dose hallucinogen exposure in human research). The reported potential risks of hallucinogen exposure include: (1) panic or fear reactions resulting in dangerous behavior during the time of drug action; (2) precipitation or exacerbation of enduring psychiatric conditions; (3) long-lasting perceptual disturbances and (4) development of an abusive pattern of hallucinogen use (Abraham, et al., 1996; Halpern and Pope, 1999; Johnson, et al., 2008).

The generalizability of the results of the present study is limited by the study population, a group of hallucinogen-naïve, well-educated, psychologically stable, mostly middle-aged adults, most of whom reported at least weekly participation in religious or spiritual activity. It would be particularly interesting to determine whether volunteers who identified as atheist or agnostic would be as likely to have mystical-type experiences and whether they would ascribe spiritual significance to such experiences. It would also be interesting to compare hallucinogen-naïve volunteers with past users to provide information about whether the novelty of effects in naïve volunteers contributes to the high persisting ratings of personal meaning and spiritual significances.

Overall, the present study shows that psilocybin can dose-dependently occasion mystical-type experiences having persisting positive effects on attitudes, mood, and behavior. The observations that episodes of extreme fear, feeling trapped, or delusions occur at the highest dose in almost 40% of volunteers, that anxiety and fear have an unpredictable time-course across the session, and that an ascending sequence of dose exposure may be associated with long-lasting positive changes have implications for the design of therapeutic trials with psilocybin. Considering the rarity of spontaneous mystical experiences in the general population, the finding that more than 70% of volunteers in the current study had “complete” mystical experiences suggests that most people have the capacity for such experiences under appropriate conditions and, therefore, such experiences are biologically normal.

Acknowledgments

Conduct of this research was supported by grants from the Council on Spiritual Practices, the Heffter Research Institute, and the Betsy Gordon Foundation. Effort for Roland Griffiths, Ph.D. in writing this paper was partially provided by NIH grant RO1DA03889. We thank David Nichols, Ph.D. for synthesizing the psilocybin, Mary Cosimano, M.S.W. for her role as a primary session monitor, Maggie Klinedinst for data management, and Linda Felch M.A. and Paul Nuzzo, M.A. for statistical analyses. We also thank Larry Carter, Ph.D., Ryan Lanier, Ph.D., Benjamin McKay, Chad Ressig, Ph.D., and Ryan Vandrey, Ph.D. for serving as assistant session monitors. The study was conducted in compliance with United States laws.

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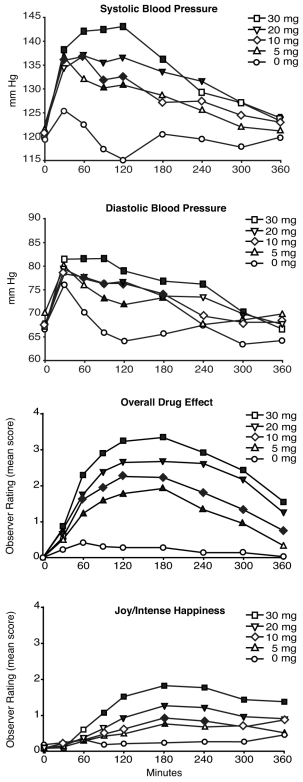

Fig. 1.

Within session time-course of psilocybin. Systolic and diastolic blood pressure and monitor ratings of overall drug effect, and joy/intense happiness as a function of time since capsule ingestion (time 0 = before drug administration). Data points are means; filled data points indicate a significant difference from 0 mg/70 kg at the indicated time point (Planned Comparisons).

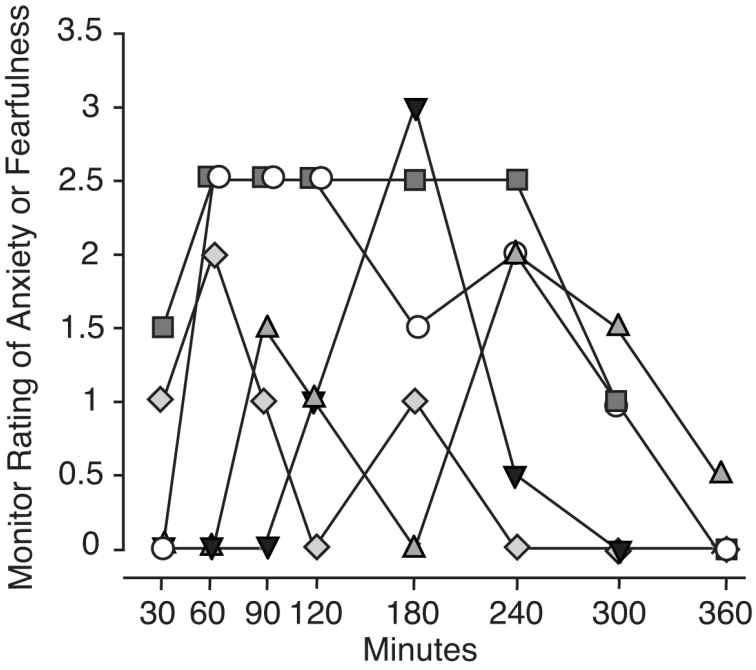

Fig. 2.

Time-course of monitor ratings of anxiety or fearfulness after 30 mg/70 kg in the five volunteers whose mean ratings were 2.0 or higher at one or more time point. Data points are mean ratings of the two session monitors. Different symbols represent different volunteers. The figure illustrates the unpredictable time-course of anxiety or fear across the session.

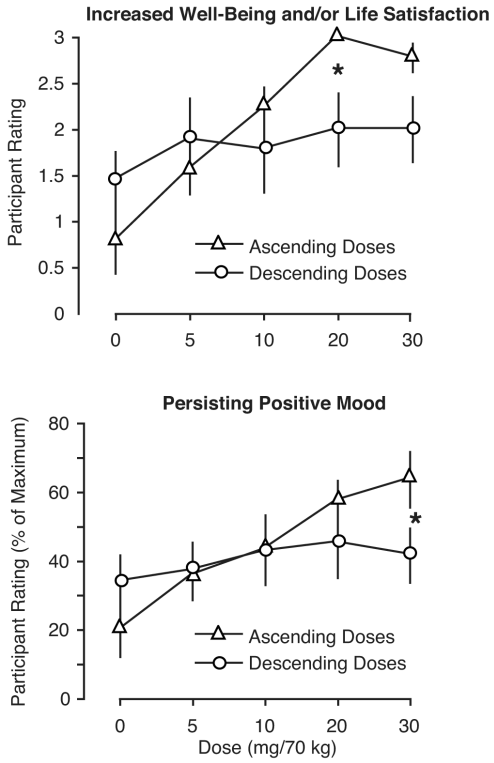

Fig. 3.

Effects of dose sequence on ratings of persisting effects of well-being/life satisfaction and positive mood completed one month after sessions. Data points are means and brackets show 1 SEM for participants in the ascending dose sequence (triangles) and the descending dose sequence (circles). Dose x Dose Sequence interactions were significant. Asterisks indicate a significant difference between the ascending and descending dose sequence at the indicated dose (Fisher's LSD post hoc).

Table 1

Cardiovascular measures and monitor ratings of volunteer behavior and mood assessed throughout the session*

Measure	Psilocybin Dose (mg/70 kg)				
	0	5	10	20	30
Cardiovascular Measures (peak effects)					
Systolic blood pressure (mm Hg)	132.6 (3.6)	**143.3 (4.3)[a]**	**145.7 (4.6)[a]**	**145.7 (4.2)[a]**	**153.1 (4.2)[b]**
Diastolic blood pressure (mm Hg)	77.5 (1.9)	**83.4 (2.1)[a]**	**83.9 (2.0)[a]**	**84.3 (2.5)[a]**	**88.8 (2.4)[b]**
Heart rate (beats per minute)	74.8 (2.5)	78.7 (2.7)[a]	77.9 (2.0)[a]	**81.2 (3.0)[a,b]**	**83.0 (2.4)[b]**
Monitor Ratings (peak effects, max score=4)					
Overall drug effect	0.69 (0.15)	**2.03 (0.13)[a]**	**2.44 (0.19)[b]**	**3.06 (0.15)[c]**	**3.42 (0.15)[c]**
Sleepiness/sedation	1.11 (0.22)	0.69 (0.18)	0.78 (0.20)	0.58 (0.16)	0.58 (0.14)
Unresponsive to questions	0.17 (0.09)	**0.19 (0.12)[a]**	**0.44 (0.14)[b]**	**0.97 (0.30)[c]**	**1.14 (0.24)[d]**
Anxiety or Fearfulness	0.28 (0.10)	**0.61 (0.19)[a]**	**0.75 (0.15)[b]**	**1.06 (0.22)[c]**	**1.19 (0.22)[d]**
Stimulation/arousal	0.53 (0.19)	**1.19 (0.13)[a]**	**1.64 (0.19)[b]**	**1.97 (0.20)[b,d]**	**2.17 (0.22)[c,d]**
Distance from ordinary reality	0.75 (0.17)	**1.92 (0.19)[a]**	**2.36 (0.21)[b]**	**2.97 (0.17)[c]**	**3.22 (0.15)[c]**
Ideas of reference/paranoid thinking	0.03 (0.03)	0.00 (0.00)[a]	0.08 (0.05)[a]	0.14 (0.06)[a]	**0.44 (0.14)[b]**
Yawning	0.22 (0.10)	0.53 (0.15)[a]	**0.97 (0.27)[a,b]**	**1.36 (0.37)[b,c]**	**1.81 (0.39)[c]**
Tearing/crying	0.61 (0.24)	**1.00 (0.29)[a]**	**1.25 (0.26)[b]**	**1.50 (0.33)[c]**	**1.81 (0.24)[d]**
Nausea	0.00 (0.00)	**0.33 (0.10)[a]**	**0.42 (0.15)[b]**	**0.31 (0.13)[c]**	**0.47 (0.13)[d]**
Spontaneous motor activity	0.22 (0.09)	0.64 (0.15)[a]	**0.78 (0.20)[a]**	**1.14 (0.32)[a,c]**	**1.47 (0.35)[b,c]**
Restless/fidgety	0.17 (0.07)	**0.44 (0.18)[a]**	**0.58 (0.12)[b]**	**0.89 (0.19)[c]**	**0.81 (0.17)[d]**
Joy/Intense happiness	0.64 (0.19)	1.19 (0.22)[a]	**1.42 (0.27)[a,b]**	**1.81 (0.33)[b,c]**	**2.14 (0.31)[c]**
Peace/harmony	0.78 (0.19)	**1.39 (0.22)[a]**	**1.64 (0.22)[a,b]**	**2.11 (0.30)[b]**	**2.03 (0.27)[b]**
Monitor Ratings (total duration in minutes, max score=360)					
Talking with monitor	85.94 (7.32)	85.42 (6.90)	83.06 (8.08)	83.75 (10.29)	85.03 (11.32)
Physical contact with monitor †	21.64 (7.26)	**35.61 (9.33)[a]**	**45.00 (12.05)[b]**	**69.94 (21.31)[c]**	**86.00 (21.15)[d]**
Sleep	13.72 (6.80)	3.83 (3.31)	2.67 (1.99)	3.42 (2.13)	0.61 (0.44)
Strong anxiety	0.33 (0.34)	0.61 (0.63)	1.14 (0.69)	1.81 (0.80)	11.11 (6.75)

* Data are means with 1 SEM shown in parentheses (N=18); within a row, bold font indicates significant difference from 0 mg/70 kg; for active doses, values not sharing a common letter are significantly different (Fisher's LSD $p<0.05$)

† e.g., reassuring touch

Table 2

Volunteer ratings on three subjective effects questionnaires completed 7 hours after drug administration*

Questionnaire and Subscale Description	Psilocybin Dose (mg/70 kg)				
	0	**5**	**10**	**20**	**30**
Hallucinogen Rating Scale					
Intensity	0.94 (0.17)	**1.85 (0.15)[a]**	**2.50 (0.14)[b]**	**2.64 (0.15)[b]**	**2.69 (0.13)[b]**
Somaesthesia	0.35 (0.07)	**1.32 (0.14)[a]**	**1.56 (0.16)[a]**	**1.91 (0.17)[b]**	**2.12 (0.15)[b]**
Affect	0.93 (0.11)	**1.48 (0.16)[a]**	**1.76 (0.16)[a,b]**	**1.95 (0.14)[b,c]**	**2.16 (0.16)[c]**
Perception	0.23 (0.07)	**1.14 (0.16)[a]**	**1.38 (0.18)[a]**	**1.72 (0.17)[b]**	**2.09 (0.20)[c]**
Cognition	0.70 (0.14)	**1.33 (0.20)[a]**	**1.63 (0.18)[a]**	**2.08 (0.19)[b]**	**2.26 (0.22)[b]**
Volition	1.04 (0.08)	**1.52 (0.12)[a]**	**1.69 (0.11)[a,b]**	**1.79 (0.12)[b]**	**1.81 (0.16)[b]**
APZ Questionnaire					
OSE (oceanic boundlessness)	2.67 (0.56)	**5.72 (0.76)[a]**	**5.89 (0.76)[a,c]**	**7.22 (0.70)[b,c]**	**8.33 (0.73)[b]**
AIA (dread of ego dissolution)	0.50 (0.24)	**2.50 (0.79)[a]**	**3.11 (0.65)[a,c]**	**4.17 (0.61)[b,c]**	**4.89 (0.84)[b]**
VUS (visionary restructuralization)	1.78 (0.48)	**6.06 (0.82)[a]**	**7.28 (0.64)[a,b]**	**7.67 (0.68)[b]**	**8.44 (0.82)[b]**
Addiction Research Center Inventory (ARCI)					
PCAG (sedative)	5.28 (0.50)	6.28 (0.87)	7.22 (0.81)	6.78 (0.80)	7.22 (0.96)
BG (amphetamine/self-control)	4.94 (0.36)	4.83 (0.38)	5.56 (0.60)	5.06 (0.55)	4.72 (0.53)
A (amphetamine)	2.78 (0.35)	**4.94 (0.39)**	**5.17 (0.52)**	**4.83 (0.48)**	**5.06 (0.62)**
MBG (euphoria)	5.61 (0.86)	8.11 (1.05)	8.06 (0.84)	7.89 (0.90)	8.28 (1.13)
LSD (hallucinogen/dysphoria)	2.56 (0.29)	**6.06 (0.64)[a]**	**6.39 (0.64)[a,c]**	**7.39 (0.65)[b,c]**	**7.83 (0.57)[b]**

*Data are mean scores with 1 SEM shown in parentheses (N=18); within a row, bold font indicates significant difference from 0 mg/70 kg; for active doses, values not sharing a common letter are significantly different (Fisher's LSD $p<0.05$)

Table 3

Volunteer ratings on two mystical experience questionnaires completed 7 hours after drug administration and at 14 month follow-up*

Questionnaire and Subscale Description	7 Hours after Drug Administration — Psilocybin Dose (mg/70 kg)					14 Month Follow-up (30 mg/70 kg) ‡
	0†	5†	10†	20†	30†	
States of Consciousness Questionnaire						
Internal unity	15.2 (4.6)	**38.0 (6.7)[a]**	**44.6 (5.07)[a]**	**64.4 (6.0)[b]**	**70.2 (6.2)[b]**	**76.5 (6.4)**
External unity	12.4 (3.7)	**32.6 (6.0)[a]**	**35.0 (6.0)[a]**	**53.3 (5.6)[b]**	**60.7 (6.7)[b]**	**63.5 (7.4)**
Sacredness	23.7 (5.5)	**48.7 (6.9)[a]**	**54.0 (6.4)[a]**	**71.1 (5.8)[b]**	**77.1 (6.4)[b]**	**83.3 (4.7)**
Noetic Quality	19.4 (5.3)	**47.5 (6.7)[a]**	**54.4 (5.8)[a,b]**	**65.3 (6.0)[b,c]**	**70.6 (6.5)[c]**	**76.9 (6.4)**
Transcendence of time and space	18.3 (4.8)	**40.4 (6.8)[a]**	**44.4 (5.6)[a]**	**65.4 (6.2)[b]**	**78.2 (5.2)[c]**	**82.6 (5.2)**
Deeply felt positive mood	26.8 (4.7)	**47.6 (5.4)[a]**	**57.5 (6.3)[a,b]**	**68.3 (5.5)[b,c]**	**73.2 (6.5)[c]**	**77.3 (5.7)**
Ineffability	19.3 (6.0)	**48.4 (6.3)[a]**	**59.1 (5.8)[a]**	**73.1 (6.6)[b]**	**81.3 (6.0)[b]**	**81.1 (4.6)**
Total	21.0 (4.7)	**45.1 (5.9)[a]**	**52.0 (5.2)[a]**	**68.3 (5.0)[b]**	**75.6 (5.4)[b]**	**80.1 (4.9)**
Mysticism Scale						
Interpretation	57.1 (6.5)	**83.5 (5.3)[a]**	**84.1 (5.2)[a]**	**95.7 (3.7)[b]**	**99.1 (2.6)[b]**	N/A
Introvertive	54.4 (7.1)	**77.6 (6.2)[a]**	**79.7 (5.1)[a]**	**93.0 (3.7)[b]**	**97.4 (3.4)[b]**	N/A
Extrovertive	30.7 (4.7)	**48.2 (4.7)[a]**	**49.4 (5.0)[a]**	**57.1 (3.9)[b]**	**61.3 (3.8)[b]**	N/A
Total (max score=288)	142.2 (17.7)	**209.2 (15.4)[a]**	**213.2 (14.4)[a]**	**245.8 (9.0)[b]**	**257.9 (8.9)[b]**	N/A

*Data are mean scores with 1 SEM shown in parentheses (N=18); data for the States of Consciousness Questionnaire are expressed as a percentage of the maximum possible score

†Data in these columns show rating data 7 hours after the indicated dose of psilocybin; within the same row for these columns, bold font indicates significant difference from 0 mg/70 kg; for active doses, values not sharing a common letter are significantly different (Fisher's LSD $p<0.05$)

‡For the States of Consciousness Questionnaire, data in this column show ratings of the 30 mg/70 kg session experience at the 14 month follow-up; each value in this column was significantly greater than the value at 0 mg/70 kg after 7 hours (as indicated by bold font) but was not different from the value at 30 mg/kg 1 month (Fisher's LSD $p<0.05$); 14 month follow-up data were not obtained for the experience-specific version of the Mysticism Scale (indicated by N/A), although data were obtained for the Lifetime version (see text)

Table 4

Volunteer ratings of persisting effects 1 month and 14 months after sessions*

Questionnaire and Subscale Description	1 Month after Sessions — Psilocybin Dose (mg/70 kg)					14 Month Follow-up (20 or 30 mg/70 kg) ‡
	0†	5†	10†	20†	30†	
Persisting Effects Questionnaire						
Positive attitudes about life	33.3 (6.6)	**45.9 (5.6)[a]**	**50.3 (6.6)[a]**	**62.2 (5.6)[b]**	**65.9 (5.9)[b]**	68.8 (4.8)
Negative attitudes about life	0.6 (0.4)	0.8 (0.5)	1.4 (0.6)	0.8 (0.4)	0.6 (0.4)	3.2 (1.3)
Positive attitudes about self	31.9 (6.1)	**44.4 (5.4)[a]**	**46.5 (6.2)[a,c]**	**54.2 (5.5)[b,c]**	**58.9 (6.0)[b]**	61.1 (5.4)
Negative attitudes about self	0.1 (0.1)	**2.1 (0.6)[a]**	**1.5 (0.6)[a,b]**	0.7 (0.5)[b,c]	1.1 (0.4)[a,c]	2.3 (0.9)
Positive mood changes	26.8 (5.4)	36.4 (5.1)[a]	**42.9 (6.2)[a,b]**	**51.3 (5.8)[b]**	**52.7 (6.0)[b]**	55.3 (5.9)
Negative mood changes	0.3 (0.2)	0.4 (0.3)	1.1 (0.7)	0.8 (0.4)	0.2 (0.2)	1.7 (0.8)
Altruistic/positive social effects	28.3 (6.0)	**37.1 (5.3)[a]**	**42.4 (6.5)[a]**	**52.0 (5.9)[b]**	**54.6 (5.7)[b]**	54.1 (6.5)
Antisocial/negative social effects	0.2 (0.2)	1.3 (0.9)	0.9 (0.7)	1.2 (0.9)	0.8 (0.9)	2.5 (0.9)
Positive behavior changes	35.6 (8.1)	45.6 (6.4)[a]	**58.9 (8.7)[a,b]**	**57.8 (7.6)[a,b]**	**71.1 (6.7)[b]**	68.9 (5.9)
Negative behavior changes	0.0 (0.0)	2.2 (2.3)	2.2 (2.3)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Increased spirituality	31.1 (6.2)	**42.3 (6.7)[a]**	**48.2 (7.0)[a,b]**	**57.9 (6.2)[b]**	**58.3 (5.8)[b]**	71.6 (6.3)
Decreased spirituality	0.4 (0.3)	0.2 (0.2)	0.6 (0.3)	0.6 (0.4)	0.8 (0.4)	1.1 (0.6)
How personally meaningful was the experience? (max score=8)	3.33 (0.40)	**5.06 (0.36)[a]**	**5.56 (0.43)[a]**	**6.67 (0.31)[b]**	**6.67 (0.34)[b]**	7.22 (0.22)
How spiritually significant was the experience? (max score=6)	2.72 (0.35)	3.28 (0.27)[a]	**3.94 (0.32)[a,c]**	**4.67 (0.31)[b,c]**	**4.94 (0.33)[b]**	5.28 (0.23)
Did the experience change your sense of well-being or life satisfaction? (max score=3)	1.11 (0.23)	**1.72 (0.25)[a]**	**2.0 (0.25)[a,c]**	**2.5 (0.22)[b]**	**2.39 (0.21)[b,c]**	2.39 (0.22)

*Data are mean scores with 1 SEM shown in parentheses (N=18); data on attitudes, mood, altruistic/social effects, and behavior changes are expressed as percentage of maximum possible score; data for the final three questions are raw scores

†Data in these columns show rating data 1 month after the indicated dose of psilocybin; within the same row for these columns, bold font indicates significant difference from 0 mg/70 kg; for active doses (Fisher's LSD $p<0.05$), values not sharing a common letter are significantly different (Fisher's LSD $p<0.05$)

‡Data in this column show ratings at the 14 month follow-up; ratings were completed with respect to experiences during either or both the 20 and 30 mg/70 kg dose sessions (see Methods); no statistical comparison was conducted

Table 5

Percentage of volunteers endorsing specific outcomes on four persisting effects items 1 month and 14 months after sessions*

Questionnaire Items	1 Month after Sessions — Psilocybin Dose (mg/70 kg)						14 Month Follow-up (20 or 30 mg/70 kg)**
	0†	5†	10†	20†	30†	20 or 30‡	
How personally meaningful was the experience?							
Single most meaningful experience of life	0.0	0.0	5.6	16.7	**33.3**	**44.4**	**38.9**
Top 5 most meaningful, including single most	0.0	11.1	**33.3**	**77.8**	**61.1**	**77.8**	**94.4**
How spiritually significant was the experience?							
Single most spiritually significant experience of life	0.0	0.0	5.6	**27.8**	**44.4**	**61.1**	**44.4**
Top 5 most spiritually significant, including single most	11.1	11.1	**44.4**	**66.7**	**77.8**	**83.3**	**94.4**
Did the experience change your sense of well-being or life satisfaction?							
Increased well-being/life satisfaction (very much)	5.6	**27.8**	**38.9**	**72.2**	**55.6**	**77.8**	**61.1**
Increased well-being/life satisfaction (moderately or very much)	38.9	55.6	**72.2**	**83.3**	**88.9**	**94.4**	**83.3**
Your behavior changed in ways you would consider positive since the experience.							
Positive behavioral change (strong or extreme)	22.2	16.7	**50.0**	38.9	**55.6**	**55.6**	**44.4**
Positive behavioral change (moderate, strong or extreme)	33.3	50.0	61.1	61.1	**88.9**	**88.9**	88.9

*Data in table show the percentage of volunteers endorsing the specific outcome

†Data in these columns are the percentage of volunteers endorsing the specific outcome 1 month after the indicated dose of psilocybin; within the same row for these columns, bold font indicates significant difference in pair-wise comparisons to 0 mg/70 kg (Cochran's Q showed p<.001 for all variables; planned comparisons performed with Wald test; see Methods for details)

‡Data in this column are the percentage of volunteers endorsing the specific outcome 1 month after either or both the 20 and 30 mg/70 dose sessions; bold font indicates significant difference in pair-wise comparisons to 0 mg/70 kg (Cochran's Q showed p<.05 for all variables; planned comparisons performed with Wald test; see Methods for details)

**Data in this column are the percentage of volunteers at 14 month follow-up endorsing the specific outcome with respect to experiences during either or both the 20 and 30 mg/70 kg dose sessions (see Methods); each value in this column was significantly greater than the value at 0 mg/70 kg (as indicated by bold font) but was not significantly different from the value at 20 or 30 mg/kg at 1 month (Cochran's Q showed p<.05 for all variables; planned comparisons performed with Wald test; see Methods for details)

Table 6

Self-reported behavior change. Verbatim written comments about the nature of behavioral changes volunteers attributed to either or both the two highest dose psilocybin session experiences in the Retrospective Questionnaire completed at the 14-month follow-up.

Volunteer	Verbatim Comments
201	Virtually eliminated all religious practices; much more spiritual now. Accepting of my parents and have a more open and honest dialogue with them. Less judgmental and more open hearted. Taken a more active role in pursuing what I want for myself.
202	I have an increased commitment to spiritual practices; I think my heart is more open to all interactions with other people; more aware of choices, take time to pause and choose, more breaks; better boundaries at work and personal relationships
205	I have a stronger desire for devotion, have increased yoga practice and prayer. I have better interaction with close friends and family and with acquaintances and strangers… I feel more certain of my career as an author. I need less food to make me full. My alcohol use has diminished dramatically… I consider myself to be better [at self-care] now than before the study…
206	Feel closer to family and friends. Incorporating Ayurvedic theory into diet and self care. [Also changed her meditation and yoga practice]
207	More regular meditation; more mindful with family; more generous with strangers; started new yoga practice; more relaxation of pace of change
210	I feel that I relate better in my marriage. There is more empathy - a greater understanding of people and understanding their difficulties and less judgment. Less judging of myself too.
211	I take more time in nature, with art. I feel closer to children and parents. I am more comfortable with friends and acquaintances. I am more committed to my career. I eat better and have taken up dance…
213	Increased time for meditation. I think I'm even warmer towards people and more accepting. I now believe I have something important to tell people about how the universe works. I am slowing learning to give myself a break.
214	[This participant endorsed no specific behavior change, although did report an increased sense of spirituality]
215	I try to judge less and forgive more. I no longer worry about money.
217	More frequent and enjoyable meditation; more desire to connect with loving energy and have loving energy flow through me to others; less willingness to allow manipulative or abusive treatment to happen without my confronting it.
218	A greater integration of the pieces of my life; more spirit less religion; less fear of being wrong
219	More fulfilling meditation; more appreciation of and openness to others [and] my own emotional reactions
222	Less concerned with the appearance of "spirituality", while realizing more that everything is sacred. I feel more accommodating and forgiving toward both friends and strangers, and less anxious to label them or convert them to my viewpoint. I am learning to recognize and release old definitions of myself.
223	During my sessions, much was shown to me about letting go of attachment around my son. More and more, sensuality and passion and gratitude continue to unfold and deepen within me.
226	The energy experience stoked my curiosity about the spiritual awakening stimulus of kundalini [spiritual energy] and has opened a new path for me!
228	[This participant endorsed no specific behavior change, although did report a deeper appreciation of positive emotional experience and empathy]
230	I am more aware and accepting [of everyone]. I have a thousand ideas to write about and am making time and space in my life to accommodate them.